PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Washington D.C. 20231
United States of America

in its capacity as elected Office

Date of mailing (day/month/year) 05 July 1996 (05.07.96)	
International application No. PCT/NL95/00370	**Applicant's or agent's file reference** PCT 0418
International filing date (day/month/year) 26 October 1995 (26.10.95)	**Priority date** (day/month/year) 03 November 1994 (03.11.94)
Applicant SWAAK, Anthonius, Josef, Gerardus	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

30 May 1996 (30.05.96)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

G. Bähr

Telephone No.: (41-22) 730.91.11

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/NL 95/00370

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,2 171 304 (CHUGAI SEIYAKU K.K.) 28 August 1986 see the whole document ---	7-9
Y	EP,A,0 269 394 (KIRIN-AMGEN, INC.) 1 June 1988 see page 2, line 5 - line 23; claims 1-4 see page 2, line 33 - line 39 see page 2, line 45 - line 47 --- -/--	1-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 1996	15. 03. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Ryckebosch, A

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 101, no. 3, 16 July 1984 Columbus, Ohio, US; abstract no. 21611u, P. BIEMOND ET AL. 'IRON MOBILIZATION FROM FERRITIN BY SUPEROXIDE DERIVED FROM STIMULATED POLYMORPHONUCLEAR LEUKOCYTES. POSSIBLE MECHANISM IN INFLAMMATION DISEASES.' page 446; see abstract & J. CLIN. INVEST., vol. 73, no. 6, 1984 pages 1576-1579, ---	1-9
Y	ANNALS OF HEMATOLOGY, vol. 65, no. 6, December 1992 NEW YORK, N.Y., US, pages 265-268, G. VREUGDENHIL ET AL. 'IRON STORES AND SERUM TRANSFERRIN RECEPTOR LEVELS DURING RECOMBINANT HUMAN ERYTHROPOIETIN TREATMENT OF ANEMIA IN RHEUMATOID ARTHRITIS.' cited in the application see page 267, left column, line 38 - line 54 ---	1-9
P,X	ARTHRITIS & RHEUMATISM, vol. 38, no. 9(SUPPLEMENT), September 1995 NEW YORK, N.Y., US, page S288 H.R.M. PEETERS ET AL. 'EFFECT OF RECOMBINANT-HUMAN ERYTHROPOIETIN ON ANAEMIA AND DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS AND ANAEMIA OF CHRONIC DISEASE. A LONG-TERM PLACEBO-CONTROLLED DOUBLE-BLIND TRIAL.' see abstract nr. 813 -----	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/NL 95/00370

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A-2171304	28-08-86	FR-A-	2576792	08-08-86
		JP-B-	6072103	14-09-94
		JP-A-	62000032	06-01-87
		US-A-	4732889	22-03-88
EP-A-0269394	01-06-88	US-A-	5013718	07-05-91
		AU-B-	602028	27-09-90
		DE-A-	3773852	21-11-91
		IE-B-	60865	24-08-94
		JP-B-	6092316	16-11-94
		JP-A-	63159322	02-07-88
		KR-B-	9509100	14-08-95
		WO-A-	8803808	02-06-88

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PCT 0418

Box No. I TITLE OF INVENTION: Use of erythropoietin in the treatment of rheumatoid arthritis.

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Boehringer Mannheim GmbH
Sandhofer Strasse 116
D-68298 Mannheim
Germany

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(i.e. country)* of nationality: DE

State *(i.e. country)* of residence: DE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Swaak, Anthonius Josef Gerardus
Kralingseweg 322
3066 RB Rotterdam
the Netherlands

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: NL

State *(i.e. country)* of residence: NL

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Smulders, Th.A.H.J.
c/o VEREENIGDE OCTROOIBUREAUX
Nieuwe Parklaan 97
2587 BN The Hague
the Netherlands

Telephone No. 070-3500464

Facsimile No. 070-3522723

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☐ AP ARIPO Patent: KE Kenya, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☐ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☐ AM Armenia
- ☐ AT Austria
- ☒ AU Australia
- ☐ BB Barbados
- ☒ BG Bulgaria
- ☒ BR Brazil
- ☒ BY Belarus
- ☒ CA Canada
- ☐ CH and LI Switzerland and Liechtenstein
- ☒ CN China
- ☒ CZ Czech Republic
- ☐ DE Germany
- ☐ DK Denmark
- ☒ EE Estonia
- ☐ ES Spain
- ☒ FI Finland
- ☐ GB United Kingdom
- ☒ GE Georgia
- ☒ HU Hungary
- ☐ IS Iceland
- ☒ JP Japan
- ☐ KE Kenya
- ☐ KG Kyrgyzstan
- ☐ KP Democratic People's Republic of Korea
- ☒ KR Republic of Korea
- ☐ KZ Kazakhstan
- ☐ LK Sri Lanka
- ☐ LR Liberia
- ☒ LT Lithuania
- ☐ LU Luxembourg
- ☒ LV Latvia
- ☒ MD Republic of Moldova
- ☐ MG Madagascar
- ☐ MN Mongolia
- ☐ MW Malawi
- ☒ MX Mexico
- ☒ NO Norway
- ☒ NZ New Zealand
- ☒ PL Poland
- ☐ PT Portugal
- ☐ RO Romania
- ☒ RU Russian Federation
- ☐ SD Sudan
- ☐ SE Sweden
- ☐ SG Singapore
- ☒ SI Slovenia
- ☒ SK Slovakia
- ☐ TJ Tajikistan
- ☐ TM Turkmenistan
- ☐ TT Trinidad and Tobago
- ☒ UA Ukraine
- ☐ UG Uganda
- ☒ US United States of America
- ☐ UZ Uzbekistan
- ☐ VN Viet Nam

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

☐ .....
☐ .....
☐ .....
☐ .....

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of _____.
The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

See Notes to the request form

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country *(in which, or for which, the application was filed)*	Filing Date *(day/month/year)*	Application No.	Office of filing *(only for regional or international application)*
item (1) EP	03. 11. 1994 03 november 1994	94203205.3	NL
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☐ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s) : _____

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA / EP

Earlier search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:*

Country (or regional Office):	Date *(day/month/year)*:	Number:
EP	03 April 1995	94203205.3

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	3	sheets
2. description	16	sheets
3. claims	1	sheets
4. abstract	1	sheets
5. drawings	–	sheets
Total	21	sheets

This international application is accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☐ priority document(s) *identified in Box No. VI as item(s):*
5. ☒ fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☐ nucleotide and/or amino acid sequence listing (diskette)
8. ☐ other *(specify)*:

Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

H. A. M. Marsman

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant: ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
SMULDERS, Th. A.H.J.
VEREENIGDE OCTROOIBUREAUX
Nieuwe Parklaan 97
2587 BN DEN HAAG
PAYS-BAS

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	04.02.97
Applicant's or agent's file reference: PCT 0418	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL 95/00370	26/10/1995	03/11/1994

Applicant

BOEHRINGER MANNHEIM GmbH et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

H. Sonkel

Telephone No.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PCT 0418		
International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/NL 95/ 00370	26/10/1995	03/11/1994
International Patent Classification (IPC) or national classification and IPC		
A61K38/18		
Applicant		
BOEHRINGER MANNHEIM GmbH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of five sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consists of a total of _____ sheets.

3. This report contains indications and corresponding pages relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/05/1996	04.02.97
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Michael Beeck M. Beeck Telephone No.

Intern. application No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

PCT/NL95/00370

I. Basis of the report

1. This report has been drawn up on the basis of (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

[x] the international application as originally filed.

[ ] the description, pages _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____,

[ ] the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,
Nos. _____, filed with the letter of _____,

[ ] the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[ ] the description, pages _____.
[ ] the claims, Nos. _____.
[ ] the drawings, sheets/fig _____.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-4,6	YES
	Claims 5,7-9	NO
Inventive Step (IS)	Claims 1-4,6	YES
	Claims 5,7-9	NO
Industrial Applicability (IA)	Claims 1-9	YES
	Claims	NO

2. CITATIONS AND EXPLANATIONS

1) The examination has been carried out assuming that the priority has been validly claimed.

In case that the priority claim is not valid the P-document ARTHRITIS & RHEUMATISM cited in the Search Report is novelty-destroying.

2) The use of erythropoietin for the treatment of anaemia in rheumatoid arthritis is already described in documents GB-A-2171304, see the whole document, and ANNALS OF HEMATOLOGY, vol. 65, pages 265 to 268, see the summary and page 267, left column, lines 38 to 54, in particular.

Since anaemia is a symptom associated with rheumatoid arthritis or a disease activity of rheumatoid arthritis, the subject-matter of claims 5, 7, 8 and 9 - as far as claims 8 and 9 depend on claims 5 or 7 - is not novel.

3) The subject-matter of claims 1 to 4 and 6 is not ren-

dered obvious by any of the documents because according to the invention now patients can be treated who suffer from rheumatoid arthritis without having an anaemia.

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

The expression "a substance having erythropoietin-like activity" in claims 1, 5 and 7 is not clear because the person skilled in the art does not know which compounds are meant.

14Apr/ Ren

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

SMULDERS, Th. A.H.J.
VERENIGDE OCTROOIBUREAUX
Nieuwe Parklaan 97
2587 BN DEN HAAG
PAYS-BAS

Kopie in/naar — TERMIJN 25-10-96 um
- 7 AUG. 1996
Beantwoord voor. | Bericht gezonden aan dd.

WRITTEN OPINION

(PCT Rule 66)

Date of mailing (*day/month/year*)	25.07.96
REPLY DUE	within 3 months/~~days~~ from the above date of mailing

Applicant's or agent's file reference: PCT 0418		
International application No. PCT/NL 95/00370	International filing date (*day/month/year*) 26/10/1995	Priority date (*day/month/year*) 03/11/1994

International Patent Classification (IPC) or both national classification and IPC

A61K38/18

Applicant

BOEHRINGER MANNHEIM GmbH et al.

1. This written opinion is the first (first, etc.) drawn up by this International Preliminary Examining Authority.
2. This report contains indications and corresponding pages relating to the following items:
   - I [X] Basis of the opinion
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [X] Certain defects in the international application
   - VIII [ ] Certain observations on the international application
3. The applicant is hereby **invited to reply** to this opinion.

   When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

   How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

   Also For an additional opportunity to submit amendments, see Rule 66.4.
   For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*.
   For an informal communication with the examiner, see Rule 66.6.

   If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 03/03/1997.

Name and mailing address of the IPEA/ European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Michael Beeck Examiner M. Beeck Formalities officer (incl. extension of time limits) J. Lausenmeyer Telephone No.

Form PCT/IPEA/408 (cover sheet) (January 1994) (26/06/1996)

Intern. application No.
PCT/NL95/00370

WRITTEN OPINION

I. Basis of the opinion

1. This opinion has been drawn up on the basis of (Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".):

[x] the international application as originally filed.

[ ] the description, pages _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,

[ ] the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,

[ ] the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,

2. The amendments have resulted in the cancellation of:

[ ] the description, pages _____.
[ ] the claims, Nos. _____.
[ ] the drawings, sheets/fig _____.

3. [ ] This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

WRITTEN OPINION

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-9
	Claims
Inventive Step (IS)	Claims
	Claims
Industrial Applicability (IA)	Claims
	Claims

2. CITATIONS AND EXPLANATIONS

1) The examination has been carried out assuming that the priority has been validly claimed.

In case that the priority claim is not valid the P-document ARTHRITIS & RHEUMATISM cited in the Search Report is novelty-destroying.

2) The use of erythropoietin for the treatment of rheumatoid arthritis is already described in documents GB-A-2171304, see the whole document, and ANNALS OF HEMATOLOGY, vol. 65, pages 265 to 268, see the summary and page 267, left column, lines 38 to 54, in particular.

Therefore the subject-matter of claims 1 to 9 is not novel.

WRITTEN OPINION

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

The expression "a substance having erythropoietin-like activity" in claims 1, 5 and 7 is not clear because the person skilled in the art does not know which compounds are meant.

Title: Use of erythropoietin in the treatment of rheumatoid arthritis.

The invention relates to certain novel uses of the known protein erythropoietin (EPO), or substances having such activity as disclosed herein.

Erythropoietin is a humoral regulator of erythropoiesis, which stimulates the production of erythrocytes. In normal conditions it is produced in sufficient quantities in the kidneys and the liver.

In case of hypoxic shocks (such as massive blood loss) erythropoietin production needs to be increased, which means that it has to be synthesised de novo. In disease-free conditions, erythropoietin levels in circulation are extremely low.

Certain diseases or side-effects of treatments of certain diseases lead to a chronic anaemia which overcharges the capacity of erythropoietin production, or otherwise cannot be met by the body's own erythropoietin resources. These diseases include chronic insufficiency of the kidneys, anaemias associated with malignancies, neonate anaemia, chronic anaemia associated with rheumatoid arthritis (ACD), anaemia after bone marrow transplantation, aplastic anaemia, myeloplastic syndrome and various haemoglobin related diseases. Also anaemic side effects have been shown to occur in various chemotherapies and AZT-therapy.
In these cases it may be helpful to administer EPO to increase erythrocyte production.

Human EPO is available as a recombinant protein, which ensures that sufficient quantities can be produced in a very pure form.

Several studies with recombinant human erythropoietin (r-hu-Epo) have been carried out, mainly in patients who underwent renal dialysis for chronic renal failure, in which diminished production of Epo and severe anaemia requiring regular bloodtransfusions occurs. A correction of anaemia by

r-hu-Epo was shown in these cases with minimal side-effects (16,17,18). In AIDS-patients treated with Zidovudine, causing bone marrow suppression, administration of 100 U r-hu-Epo/kg thrice weekly intravenously, significantly decreased transfusion requirements (19).

The invention provides a novel use of erythropoietin which is not directly related to its erythrocyte stimulating properties.

This use is specifically clear in rheumatoid arthritis, which therefore is more specifically described as explanatory example for the invention.

Rheumatoid arthritis is an inflammatory disease of synovial membranes, usually expressing itself in a symmetrical polyarthritis. During the course of their disease 70% of rheumatoid arthritis (RA) patients develop some kind of anaemia (1), which may be due to iron deficiency (2,3), vitamin B12 deficiency or folic acid deficiency (4,5), haemolysis or adverse reactions to anti-rheumatic drugs (6,7). In addition active RA is frequently (in nearly 50%) accompanied by anaemia of chronic disease (ACD) (8).

Factors involved in the pathogenesis of ACD are ineffective erythropoiesis (9), interleukin-1 (10), tumour necrosis factor α (TNF-α) (11), decreased erythropoietin synthesis (5,12,13) and/or a decreased response to erythropoietin by the bone marrow (14,15).

So far only a few studies with r-hu-Epo have been carried out in RA patients. A haemoglobin (Hb) rise was shown in two anaemic RA patients treated with r-hu-Epo, 125-250 IU/kg thrice weekly, a significant haematocrit rise was recorded (20).

We have treated ten RA patients who suffered from ACD with recombinant human EPO.

In all RA patients a rise in haemoglobin was observed. Despite a wide range of values, the increase in haemoglobin became significant after the second week of treatment with recombinant human EPO.

Besides this expected result of EPO treatment a different unexpected benefit was obtained by the treatment.

The invention thus provides the use of erythropoietin or a substance having erythropoietin-like activity in the preparation of a pharmaceutical for the treatment of chronic inflammations, especially those related to (auto-)immune diseases, in particular RA. In RA we found an overall improvement in the clinical parameters for scoring disease activity. Most impressive are the results on clinical variables such as painscore and morning stiffness as disclosed below. A significant decrease in the number of tender joints was already observed after two weeks of treatment. The changes in other clinical parameters did not reach statistical significance due to the wide range of values and the small number of patients in the study. However, when the parameters were expressed as percentages of their baseline value, significant improvements were observed.

In addition to this effect on clinical variables a further positive effect was seen in the area of an overall sense of well-being of the treated patients.

According to the invention any erythropoietin which has the ameliorating effect on chronic inflammations can be used. Preferably this erythropoietin is not immunogenic so that it can be administered repeatedly. This will usually lead to the use of human erythropoietin of any origin, although recombinant erythropoietin seems the product of choice because of its purity and constant quality. On the other hand it may very well be possible to use non-human truncated forms of mammalian erythropoietin as long as they have the activity and are not immunogenic upon normal administration to patients. Selected mutants (longer acting, more stable), fragments or derivatives of erythropoietin may also be used as long as they fulfil both criteria.

It is worthwile to note that patients not having a kind of anaemia can thus be treated with EPO. However, caution has to be taken that Hb-levels do not rise to detrimental levels. Ways of lowering the Hb-levels are well-known in the art.

Also, it will be necessary to ensure that no hypertension occurs at a detremental leval. Ways to avoid such a reaction are also well known in the art.

One of the mechanisms through which EPO may ameliorate the disease symptoms in RA (or other chronical inflammations) is that it mobilises iron towards haemoglobin production. Iron (free and/or bound in ferritin) deposits are known to occur in the synovia of RA-affected patients. Synovial fluid iron levels correlate with RA activity and therefore it is thought that iron is involved in the initiation or maintenance of RA synovitis through mediating tissue damage. The role of iron in the pathogenesis of RA may be related to the fact that iron stimulates the production of hydroxyl radicals, which are very potent agents in the destruction of cartilage, membranes and proteins. A thorough discussion of the role and the mechanisms of iron in the inflamed joint can be found in Vreugdenhil et al. (23). In said study it is suggested to administer iron chelators to RA patients. EPO does not chelate iron. However, EPO does mobilise iron to be incorporated into haemoglobin through serum transferrin. Thus EPO may reduce the levels of iron in the synovial fluids.

Another possible mechanism which may be responsible for the unexpected beneficial effect of EPO in (especially) RA, may be found in its influence on the T_{h1}/T_{h2} balance.

One of the key functional parameters determining the outcome of immune responses, for example infectious agents, is the nature of the cytokines produced locally by immune cells. At this moment evidence is obtained that T-cells can be classified into T_{h1} and T_{h2} cells; both characterized by a different cytokine secretion profile. T_{h1} cells secrete IL-2 and TNF-γ upon activation bu not IL-4 or IL-5, and T_{h2} cells produce IL-4 and IL-5 but not IL-2 or TNF-γ. The differential cytokine profile of these CD4+T cells correlates with different effector functions exerted by these cells: T_{h1} cells mediate delayed type hypersensitivity (DTH) responses and T_{h2} provide superior help for antibody productions by B cells. There is also some support for the notion that T_{h1} and T_{h2}

cells are progency of Th_0 cells which can produce IL-2, TNF-γ, IL-4 and IL-5 simultaneously. T_{h1} like cytokine secretion profile. In different animal studies and observations in human diseases, like leprosy, evidence is obtained that the balance between T_{h1} and T_{h2} response determined the outcome of for example an infectious disease and disease manifestations.At this moment a selective activation of T_{h1}-like T cells is proposed as a hallmark of the aethiopathogenesis of rheumatoid arthritis. Evidence for this hypothesis is formed by the fact that on histopathological examination of the synovial tissue, a DTH like of inflammatory reaction is observed which is characteristic for a T_{h1} response.

Some observations in our RA patients treated with r-hu-EPO showed a rise in serum IgE levels; which is consistent with the concept that EPO can give support for a T_{h2}-like response. In other ways influencing the T_{h1}-T_{h2} balance in a more T_{h2} cytokine secretion profile. Indirect evidence for this hypothesis is formed by the fact that 2 out of 3 monoclonals raised against EPO are of the IgE class (IgE synthesis is regulated by IL-4).

When EPO is administered to new-born rats a reduced neutrophil production is observed. This reduced neutrophil production may be partly responsible for the ameliorating effect observed in our patients in that neutrophils play a key role in inflammatory reactions.

It has also been observed that EPO can in some ways counteract the activity of TNF-α. TNF-α is an important pro-inflammatory cytokine.

It may also be the case that EPO diverts the multipotent progenetor blood cells to the production of erythrocytes instead of granulocytes.

EXPERIMENTAL

Patients:

This study focused on the effects of r-hu-Epo on RA disease activity parameters. It is a part of a project studying the pathogenesis of ACD and possible therapeutic

strategies. The effect of r-hu-Epo on the anaemia and iron metabolism is reported in more detail (21).

Ten patients with RA (22) were studied, fulfilling the criteria for ACD as proposed by Carwright (8). ACD was confirmed by measuring stainable iron in a bone marrow preparation. Patients treated previously with iron, vitamin B12, folic acid and cytotoxic drugs were excluded. Other causes of anaemia were also excluded such as the presence of haematuria, positive occult bloodtest in stool, decreased creatinine clearance, haemolysis and low vitamin B12 of folic acid.

The demographic features of the studied patients are summarized in table I. All patients used a variety of non steroidal anti-inflammatory drugs.

Treatment:

Recombinant human Erythropoietin (r-hu-Epo, Boehringer, Mannheim, Germany), was administered three times a week at a dose of 240 units/kg subcutaneously at the right upper leg for 6 weeks.

Clinical and laboratory monitoring:

Detailed clinical and laboratory evaluation was performed at entry and weekly by the same physician, till the end of the study (6 weeks), then at 9 and 12 weeks after onset of the study. Routine laboratory procedures were used for assessment of haemoglobin (Hb), haematocrit (Ht), mean corpuscular volume (MCV), mean corpus haemoglobin (MCH) and reticulocytes count. Serum iron was measured spectrophotometrically (Instruchemie, Hilversum, the Netherlands). Transferrin and CRP was assessed with a nephelometer (Ablon Medical Systems, Leusden, the Netherlands) and serum ferritin by solid phase enzyme immune assay (Ferrizyme, Abbott Labs, Chigaco, USA). The erythrocyte sedimentation rate (ESR) was measured by the Westergren method. The Ritchie index, grip strength, number of swollen joints, morning stiffness and a subjective pain score (visual analogue scale, 0-10 points) were assessed as well. Liver and kidney function tests were performed to monitor possible side effects.

Data evaluation:

For evaluation all clinical data were stored and analyzed on a Wang personal computer using the Lotus 1-2-3 program. Statistical evaluation of the results was by Fishers' exact test for group differences. P values of 0.05 or less were considered significant.

RESULTS

Effect of r-hu-Epo on the anemia of chronic disease (ACD).

In all RA patents a rise in haemoglobin was observed (table II). Despite of the wide range of values, the increase in haemoglobin became significant after the second week of treatment compared to baseline values. When treatment was stopped haemoglobin stayed significant higher compared to the baseline value, but dropped in the 12th week.

Iron deficiency developed as shown by the fact that five patients were characterized by ferritin levels lower than 40 µg/ml.

Effect of r-hu-Epo on disease activity parameters.

Laboratory parameters: ESR and CRP.

A decrease in ESR was found in all patients (table III), which started at the third week of treatment and remained so until the end of the study. As illustrated the decrease in eight patients was more than 20% of their baseline value; which was highly significant. The same holds true for the CRP values, but due to the wide range in the absolute values and small number of investigated patients, no significance could be calculated. However, expressing the values as a percentage of the baseline value, also in this way after the third week of treatment, a significant decrease in the CRP levels was observed.

Subjective clinical scores: painscore (PS) and morningstiffness (MS).

Both parameters (PS and MS) showed during the follow-up a tendency to decrease (table IV). Caused by the variability in absolute values and small number of patients a significancy could not be calculated. When the values were expressed in a

percentage of the baseline value, the PS decreased significantly after the third week of treatment and the MS after the sixth week.

Objective disease activity scores: gripstrength (GS), Ritchie Index (RI) and number of swollen joints (SJ).

All parameters as shown in table V showed a continuous tendency towards improvement which lasted during, and also after, the treatment period. In the absolute changes in number of tender joints a significant decrease could be calculated from the third week of treatment. Also a continuous decrease in the number of swollen joints was observed from T3 on and at T9 nine out of ten patients had less swollen joints, which was highly significant.

Caused by the variation of the individual values of the GS, it was impossible to calculate a significance. However, when the values were expressed as a percentage of their baseline values after three weeks of treatment, a significant increase in GS was noted. It should be mentioned that the GS remained stable in three patients during our investigation.

TABLE I

Demographic features of ten patients characterized on having anaemia of chronic disease (ACD) and rheumatoid arthritis (RA)

Female/Male	9/1	
Mean age (years)	68 ± 6,5	
Treatment:		
Prednisolone	(2 patients)	5 mg
Sulphasalasine	(3 patients) (range)	1.5-2.5 g/day
Plaquenil	(1 patient)	200 mg/day
Auromyose	(1 patient)	50 mg/in 2 weeks
D-Penicillamine	(2 patients) (range)	500-750 mg/day

All patients were treated for more than 2 months with the mentioned disease modifying anti-rheumatic drugs.

TABLE II

Effect of recombinant human erythropoietin (r-hu-Epo) therapy on haemoglobin and ferritin levels at the defined time periods after onset therapy in ten patients with rheumatoid arthritis (RA)

Variable	Base-line	Values during the 6 weeks therapy and after 3 and 6 weeks of treatment.							
	TO*	T1	T2	T3	T4	T5	T6	T9	T12
Hemo-globin mmol/l ± sd	5.9 0.4	6.1 0.5	6.5** 0.6	6.8 0.7	7.0 0.9	7.2 1.0	7.2 1.0	7.2 1.1	6.6 0.9
Ferritin material µg/ml Range	216 140-318		143** 44-301				80 14-157	49 19-82	61 52-84

* Refers to treatment weeknumber.
** Marks the treatment period when the differences between baseline became significant.

TABLE III

Effect of recombinant human erythropoietin (r-hu-Epo) treatment on the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels at the defined time periods after onset therapy in ten patients with rheumatoid arthritis (RA)

Variable	Baseline	Values during 6 and 3 weeks after the end of treatment period.		
		T3*	T6	T9
ESR (mmH) mean ranges	82 42-137	61** 18-112	53** 7-98	56** 7-111
ESR (%) mean ranges	100 -	63 32-107	59 16-108	64 16-144
Number of patients with a change > 20% baseline value	-	8**	7**	8**
CRP (mg/l) mean ranges	51 10-105	45 4-113	43 3-122	44 1-144
CRP (%) mean ranges	100 -	85 17-155	85 8-204	81 5-181
Number of patients with a change > 20% baseline value	-	5**	6**	6**

* Refers to treatment weeknumber.

** Marks the treatment period when the differences compared to baseline values became significant. $P > 0.05$, Fishers's exact test.

TABLE IV

Effect of recombinant human erythropoietin (r-hu-Epo) treatment on the overall pain score (PS) and morning stiffness duration (MS) at the defined time periods after onset treatment in ten patients with rheumatoid arthritis (RA).

Variable	Baseline	Values during 6 and 3 weeks after the end of treatment period.		
		T3*	T6	T9
PS mean ranges	3.9 2.7	3.0 1-5	2.7 1-5	2.8 1-5
PS (%) mean ranges	100 -	82 50-150	70 33-150	73 33-100
Number of patients with a change > 20% baseline value	-	7**	8**	6**
MS (min) mean ranges	45 10-120	37 10-120	35 10-120	36 10-120
MS (%) mean ranges	100 -	88 50-150	78 50-150	85 50-150
Number of patients with a change > 20% baseline value	-	3	5**	5**

* Refers to treatment weeknumber.
** Marks the treatment period when the differences compared to baseline values became significant.
P > 0.05, Fishers's exact test.

TABLE V

Effect of recombinant human erythropoietin (r-hu-Epo) treatment on the Ritchie index (RI), number of swollen joints (SJ) and grip strenght (GS) at the defined time periods after onset treatment in ten patients with rheumatoid arthritis (RA).

Variable	Baseline	Values during 6 and 3 weeks after the end of treatment period.		
		T3*	T6	T9
RI mean ranges	13 3-38	10.2 1-22	7.7** 1-14	6** 2-13
RI (%) mean ranges	100 -	66 25-100	62 33-111	56 22-95
Number of patients with a change > 20% baseline value	-	8**	7**	9**
SJ mean ranges	8 6-5	6 3-11	4.5 2-8	4.5 1-9
SJ (%) mean ranges	100 -	72 42-100	61 37-100	51 20-100
Number of patients with a change > 20% baseline value	-	8*	7*	9*
ESR (mmH) mean ranges	72 15-190	87 20-220	91 20-220	90 15-220
ESR (%) mean ranges	100 -	112 90-133	118 90-166	118 90-166
Number of patients with a change > 20% baseline value	-	4**	4**	5**

* Refers to treatment weeknumber.

** Marks the treatment period when the differences compared to baseline values became significant.

P > 0.05, Fishers's exact test.

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CLAIMS

1. Use of erythropoietin or a substance having erythropoietin-like activity in the preparation of a pharmaceutical for the treatment of chronic inflammations.

2. Use according to claim 1, wherein the inflammation is associated with an immune disease.

3. Use according to claim 2 wherein the immune disease is an auto-immune disease.

4. Use according to claim 3, wherein the auto-immune disease is rheumatoid arthritis.

5. Use of erythropoietin or a substance having erythropoietin-like activity in the preparation of a pharmaceutical for the treatment of symptoms associated with rheumatoid arthritis.

6. Use according to claim 5, wherein the symptoms treated comprise at least one of the group of morning stiffness, painful and swollen joints, loss of grip strength and pain.

7. Use of erythropoietin or a substance having erythropoietin-like activity in the preparation of a pharmaceutical for the amelioration of disease activity of rheumatoid arthritis.

8. Use according to anyone of the afore going claims, wherein the erythropoietin is human erythropoietin.

9. Use according to anyone of the aforegoing claims wherein the erythropoietin or the substance having such activity is of recombinant origin.